

Childhood Asthma and Passive Smoking

Urinary Cotinine as a Biomarker of Exposure¹⁻³

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Introduction

Despite a number of epidemiologic investigations, the relation between childhood asthma and passive smoking remains uncertain. Prospective studies of general populations have failed to demonstrate an increased incidence of diagnosed asthma among the children of smokers, although an increase in parent-reported wheezing is apparent (1-5). Some cross-sectional studies have demonstrated an association between parental smoking and asthma (6, 7) or wheezing (8-10); others have failed to find such relations (11-13). In studying a group of asthmatic children, Murray and Morrison showed that maternal smoking increases the severity of the disease and bronchial hyperreactivity (14-16). An increase in the number of emergency room visits among asthmatic children from smoking households has been demonstrated in one study (17). The question of whether passive smoking triggers acute attacks of asthma has not yet been specifically addressed.

Exposure misclassification may be one reason for the inconsistency among epidemiologic studies. The studies conducted thus far have relied on questionnaire measurement of passive smoking, which may inadequately reflect the child's dose of environmental tobacco smoke. In general, exposure misclassification reduces the chances of observing a difference in asthma between exposed and unexposed children.

The aim of this study was to test two hypotheses: first, passive smoking is a risk factor for the asthmatic state, and second, recent passive smoke exposure acts as a trigger of acute attacks of asthma. To provide a more objective determination of exposure to tobacco smoke, we measured cotinine in the urine of these children. Cotinine is a metabolite of nicotine, with an elimination half-life of about 20 to 40 h (18). Among nonsmok-

SUMMARY To assess the relationship between passive smoking and asthma, we investigated (1) whether passive smoking was more prevalent among asthmatic than control children and (2) whether exposure to tobacco smoke was higher in acute asthma than in nonacute asthma. Three groups were recruited into a case-control study: 72 acute asthmatic children from the emergency room (ER), 35 nonacute asthmatic children from the asthma clinic, and 121 control children from the ER. Both questionnaire and urinary cotinine/creatinine ratio (CCR) were used to assess passive smoking. Levels of CCR > 30 ng/mg were used to identify children exposed at home. Mean CCR was also computed. Acute and nonacute asthmatic children had similar prevalences of passive smoking at home. Acute cases showed a higher mean CCR than nonacute cases, but this was not significant. Comparing all asthmatic to control children, smoking by the maternal caregiver was more prevalent among asthmatic children (odds ratio OR = 2.0, 95% CI 1.1, 3.4). This was confirmed by CCR > 30 ng/mg (OR = 1.8, 95% CI 1.04, 3.35) and by the difference in mean CCR (43.6 versus 25.8 ng/mg, $P = 0.06$). We conclude that smoking by the maternal caregiver is associated with clinically significant asthma in children. We could not show that it is a trigger of acute asthma attacks.

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ing children, it has been shown to be correlated with maternal smoking and with the number of smokers at home (18, 19).

Methods

A case-control study was conducted from October 1988 through April 1989 in a New York City medical center. The study population comprised inner city children aged 3 to 14 yr attending the pediatric emergency room (ER) or the pediatric asthma clinic at the hospital. The ER functions as both a walk-in clinic and an emergency room.

Cases of acute asthma were ascertained from children presenting to the ER on weekdays. The definition of a case of acute asthma required (1) a physician diagnosis in the ER of acute airflow obstruction requiring bronchodilator therapy, and (2) at least one previous episode of physician-diagnosed acute asthma as reported by the accompanying adult.

A second case group, consisting of children whose asthma was not acute, was recruited from all children aged 3 to 14 yr attending the asthma clinic during the period of study. These children all had a history of episodic or chronic airflow obstruction requiring some form of bronchodilator therapy. Any child (1) who had suffered an attack of acute asthma resulting in a visit to a doctor or school absence during the previous 2 wk or (2) who

required treatment during that visit to the clinic was excluded.

The control group comprised children attending the ER during the period of the study with any presentation other than acute asthma. The accompanying adult was interviewed about demographic characteristics (age of child, sex, ethnic group, parental occupation, and years of schooling completed by parents), pets, recent history of asthma and other illness (including recent upper respiratory infection), use of asthma medication, and smoking habits of the maternal caregiver (mother or other primary caregiver) and oth-

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er household members. Gas stove use was not included because a pilot study found gas use to be almost universal in this population. Children aged 10 to 14 yr were taken aside by the interviewer, who inquired whether the child had ever tried smoking, and if so, whether he or she had smoked recently. Chart review was undertaken to exclude subjects who did not meet study criteria and to determine asthma medication.

An upper respiratory infection (URI) was defined as the occurrence during the previous week of any two of a list of four symptoms. These included (1) a runny nose not "usual" nor "frequent" for that child (to distinguish acute infection from allergic symptoms), (2) sneezing, also not usual nor frequent, (3) sore throat, and (4) sore or discharging ears. Alternatively, if the adult reported fever in the child or a cold in another household member in the previous week, only one of the four symptoms was needed to define a URI.

Noncompliance was defined as having missed one or more doses of asthma medication during the previous week if the child was on a prescribed daily regimen. An index of socioeconomic status (SES) was computed from the occupational category and years of education of the parent(s) with whom the child resided (Hollingshead A.B. Four factor index of social status. Department of Sociology, Yale University, 1975). Parents or guardians were classified into three categories: (I) unskilled, semiskilled, or not formally employed; (II) skilled, clerical, or sales; or (III) technical, professional, or business. The 6 months of the study were classified by average monthly temperature (recorded by the New York Meteorological Service) into cool months (October, November, and April) or cold months (December, February, and March).

The smoking status of the maternal caregiver (current, ex, or never) and of each household member (current or not) was re-

corded. Number of cigarettes smoked daily was coded into four intervals (1 to 5, 6 to 15, 16 to 20, and > 20). The total number of cigarettes smoked daily by all household smokers was expressed as a continuous variable by summing representative numbers for each of the four intervals (2, 10, 20, and 25, respectively).

A urine specimen was collected from each child at the time of the interview. Within 2 h it was deep frozen until transfer to the laboratory. Urinary cotinine concentration was determined by competitive inhibition radioimmunoassay using rabbit cotinine antiserum and tritiated cotinine (20). To adjust for the effect of variable dilution on the spot concentration of cotinine, urinary creatinine was measured and the cotinine/creatinine ratio (CCR) was calculated.

Because the frequency distribution of the CCR values was highly nonnormal, being skewed to the right, CCR values were analyzed in two ways. First, Henderson and colleagues (21) reported that a cutoff CCR level of 30 ng/mg identifies children exposed at home with a high degree of sensitivity (80%) and specificity (100%). This level was therefore used to categorize subjects into exposed and unexposed. Second, logarithmic transformation of CCR produced a bimodal distribution with one peak at the zero or non-detectable level and a log normal distribution of the remaining values. Owen and DeRouen (22) have shown that a function proposed by Aitchison (the Aitchison estimator) provides best estimates of the mean and variance of such a distribution. These statistics were estimated for grouped CCR values and a z test applied to differences between groups.

The role of possible confounding or effect-modifying variables, such as age, sex, and ethnicity, were examined by stratified analysis. (Effect modification refers to significant variation of the odds ratio with different levels of a third variable, such as sex. For example,

the association between passive smoking and asthma might be observed among boys but not among girls). Multivariate analysis was performed using the BMDP statistical software for logistic regression via SAS (SAS Institute Inc., Release 5.18, March 1989).

This study was approved by the institutional review board of the hospital, and informed consent was obtained for each participant.

Results

A total of 271 parents or guardians were approached in the ER and asthma clinic, of whom 244 (90%) gave informed consent. Response rates by group were acute asthma (88%), asthma clinic (98%), and ER control (88%). Fourteen asthmatic and two control subjects were rejected on chart review for failing to meet study criteria (e.g., no previous asthma among acute asthmatic cases or an attack in the prior 2 wk among clinic cases). This left 228 children in the study: 72 acute asthmatic children, 35 children from the asthma clinic, and 121 ER control children. Urine was not obtained from 14 of these, leaving 214 for cotinine analysis. The mother was the study respondent for 181 children (79%); for the remainder the father, grandmother, or aunt provided the information. For 18% of children, someone other than the biologic mother was the primary caregiver, usually the grandmother. In 55% the father did not live at home. Among the controls, 35% had respiratory diagnoses identified on chart review (including ear, nose, and throat), 8% "viral syndrome" and 12% trauma or soft tissue diagnoses; 45% had other medical diagnoses (abdominal, eyes, skin, neurologic, others), including some with no clear diagnosis.

Acute Versus Nonacute Asthmatic Children

Demographic and medical features of acute asthma and nonacute asthma are displayed in table 1. The two groups were similar in age, sex, and SES. African-American children were overrepresented in the acute group. Recent URI was markedly more common among the acute asthmatic children, with an odds ratio (OR) of 2.5 (95% confidence interval, 1.1, 5.6).

With regard to pattern of medical care, most of the children in both groups previously made use of the ER for acute asthma. A smaller percentage (65%) of the acute asthmatic children previously attended the asthma clinic. Among those children on a daily medication regimen, there was no difference in the proportions missing one or more doses in the previous week. However, the asthma clinic

TABLE 1
ACUTE VERSUS NONACUTE ASTHMA: SAMPLE CHARACTERISTICS

Factor	Acute Asthma (n = 72)	Nonacute Asthma (n = 35)
Age, yr	7.0 (3-14)	7.9 (3-14)
Sex (male), %	53	60
Ethnicity, %		
Hispanic	60	66
African-American	37	26
Other	3	9
SES, %*		
I	63	66
II	18	20
III	19	14
URI, %*	69	47†
Previous use of ER for acute asthma, %	97	86‡
Any previous attendance at asthma clinic, %	65	100§
Daily asthma medication, %	36	80§
Missed any dose in previous weeks*, %	16	14

* See text for definition.

† Odds ratio (OR) = 2.5 (1.1, 5.6); p = 0.03.

‡ p = 0.02.

§ p = 0.000.

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TABLE 2
ACUTE VERSUS NONACUTE ASTHMA: EXPOSURE VARIABLES

Factor	Acute Asthma (n = 72)	Nonacute Asthma (n = 35)
Any smoker at home, %	53	57
Daily cigarettes by all smokers, mean \pm SD (standard deviation)	7.7 \pm 11.8	10.7 \pm 14.6
Maternal caregiver currently smokes, %	40	51*
CCR \geq 30 ng/mg, %	38	39†
Mean CCR, ng/mg, %‡	46.2 \pm 98.3	38.5 \pm 74.1§
Hispanic	40.9 \pm 13.3	34.4 \pm 14.7
African-American	57.4 \pm 28.9	59.2 \pm 41.7

* Odds ratio = 0.6 (0.28, 1.43), p = 0.2.

† Odds ratio = 0.9 (0.38, 2.19), p = 0.8.

‡ Arcthoson transformation; see METHODS.

§ p = 0.06.

TABLE 3
ASTHMA VERSUS CONTROL: SAMPLE CHARACTERISTICS

Factor	Asthma (n = 107)	Control (n = 121)
Age, yr	7.3 (3-14)	7.5 (3-14)
Sex (male), %	62	59
Ethnicity, %		
Hispanic	62	72
African-American	34	28*
Other	5	1
SES, %†		
I	64	66
II	19	19
III	18	15
URI, %‡	62	62
Month, %		
October/November/April (cool)	55	40‡
December/February/March (cold)	45	60

* p = 0.06.

† See text for definition.

‡ p = 0.02.

TABLE 4
ASTHMA VERSUS CONTROL: EXPOSURE VARIABLES

Factor	Asthma (n = 107)	Control (n = 121)
Any smoker at home, %	54	51
Daily cigarettes by all smokers, mean \pm SD	8.7 \pm 12.8	6.1 \pm 10.3
Maternal caregiver smokes, %	44	28*
CCR \geq 30 ng/mg, %	38	25†
Mean CCR, ng/mg‡	43.6 \pm 87.7	25.8 \pm 46.5§

* Odds ratio = 2.0 (1.1, 3.4), p = 0.03.

† OR = 1.9 (1.04, 3.35), p = 0.04.

‡ Arcthoson transformation; see METHODS.

§ p = 0.06.

group had a much larger proportion on such a daily regimen. There was no difference between the groups in pet ownership or month of recruitment.

The passive smoke exposure of the two groups is compared in table 2. There was no significant difference in general household smoking. Smoking by the maternal caregiver was more common in the nonacute group. There was no difference in the proportions of children exposed at home as defined by CCR levels at or above 30 ng/mg. The mean CCR was nonsignificantly greater in the acute

group (46.2 ng/mg) than among the nonacute children (38.5 ng/mg).

Because the two asthma groups were similar with regard to demographic characteristics, smoking prevalences, and past ER use, they were combined into a single asthmatic group for comparison with the control group.

Asthmatic Versus Control Groups

The asthmatic and control groups are similar with respect to age, sex, SES, and recent URI, as shown in table 3. There was a significant difference in month of

recruitment, with asthmatics enrolled in higher proportion than control subjects in the cool months of October, November, and April compared with the cold months. There was also a greater proportion of African-American children among those with asthma. There was no difference in ownership of household pets.

Comparing smoking variables (table 4), there was no significant difference in the proportions having any smokers at home or in daily cigarette consumption by all smokers. The maternal caregiver, however, was much more likely to smoke among the asthmatic group (OR = 2.0). This was confirmed by the differences in CCR, whether defined categorically (OR = 1.9) or quantitatively (mean 43.6 versus 25.8 ng/mg).

When analysis was restricted to those children (n = 181) whose maternal caregiver was their biologic mother, the same association between maternal smoking status and asthma was found. This was so whether maternal smoking was defined as (1) current smoking by the biologic mother [OR = 1.9 (95% confidence interval 1.1, 3.6)], (2) current or exsmoking [OR = 2.0 (1.1, 3.8)], or (3) smoking in pregnancy [OR = 1.9 (1.1, 3.5)].

Ethnicity and month of recruitment were examined as potential confounders. African-American children had a slightly higher mean CCR (38.9 ± 9.4 ng/mg) than Hispanic children (32.6 ± 5.16 ng/ml), and they showed no significant difference on the categorical CCR measure [OR = (0.7-2.5)].

Regarding month of recruitment, there was no difference in CCR between the cool and cold months, whether measured categorically or quantitatively. On entering CCR (≥ 30 ng/mg), month, and ethnicity simultaneously into a logistic regression model, the association between CCR and asthma was altered only slightly, increasing the odds ratio from 1.9 to 2.0.

Boys showed a stronger association between maternal smoking and CCR (≥ 30 ng/mg) and their asthma than did girls. The differences were not statistically significant, however.

To remove the influence of extreme values, the analysis was repeated excluding the three CCR outliers greater than 200 ng/mg. The results were essentially unchanged.

The analysis was repeated using only acute asthmatic subjects as the case group (table 5). The pattern was similar to that of table 4, except that the odds ratios were slightly smaller, and no longer significant at the 0.05 level, for the comparison of

TABLE 5
ACUTE ASTHMA VERSUS CONTROL: EXPOSURE VARIABLES

Factor	Acute Asthma (n = 72)	Control (n = 121)
Any smoker at home, %	53	51
Daily cigarettes by all smokers, mean \pm SD	7.7 \pm 11.8	6.1 \pm 10.3
Maternal caregiver smokes, %	40	28*
CCR > 30 ng/mg, %	38	25†
Mean, CCR, ng/mg‡	46.2 \pm 98.3	25.8 \pm 46.5§

* Odds ratio = 1.7 (0.92, 3.15), p = 0.06.

† Odds ratio = 1.8 (0.94, 3.50), p = 0.07.

‡ Archison transformation, see METHODS.

§ p = 0.11

maternal smoking and CCR measured categorically. The mean difference in CCR between acute asthmatic and control children was 46.2 versus 25.8 ng/mg, was also non-significant.

The association of CCR (\geq 30 ng/mg) with questionnaire measures of exposure was computed. CCR was most strongly associated with the maternal caregiver's smoking status [OR = 11.9 (6.3, 22.3)]. Association with smoking by household smokers other than the maternal caregiver was lower [OR = 3.4 (1.3, 8.7)]. To examine further whether smoking by the maternal caregiver was mainly a surrogate for the total number of smokers in the home, the correlation of smoking by maternal caregiver with number of other smokers was calculated. There was little correlation (Spearman's coefficient = 0.1; p = 0.13). CCR thus accorded most closely with current smoking by the maternal caregiver as an independent source of passive smoking by the child.

None of the children questioned admitted to smoking. Active smoking by the child could be a confounder of the association between passive smoking and

asthma. If recent, it should account for CCR levels at the high end of the distribution. These possibilities were explored by examining the characteristics of those children with high CCR values ($>$ 100 ng/mg) (table 6). The ages of these children were mostly at the low end of the age range, making it highly unlikely that active smoking explains most of these values. Further, they were evenly divided between cases and controls, so that even if all were attributable to active smoking the error would not be systematic.

Discussion

We found that passive smoking is associated with clinically significant childhood asthma in a sample of children drawn from an inner city population of mainly Hispanic and African-American children using a hospital's ambulatory care services.

The comparability of the groups needs to be considered. Controls in our study were drawn from the pediatric ER and can be regarded as sampling the population of children who use the ER. There

were no confounding demographic differences between control and asthmatic children. The asthma clinic subjects, although not drawn from the ER, previously used the ER in 86% of cases, making it unlikely that they differed markedly from acute asthmatic or control children in their pattern of use of the ER for acute illnesses.

Among children using the ER with diagnoses other than acute asthma, a large proportion present with respiratory symptoms. Passive smoking has been shown to be associated with acute respiratory infection in younger children and chronic respiratory symptoms in older children (23). Our control group therefore probably had more passive smoke exposure than would be found in a comparable group of community controls. If so, we would be less likely to observe a difference in passive smoking between control and asthmatic children in this study. The fact that an effect was nonetheless found strengthens its validity.

Smoking by the maternal caregiver was the exposure variable most strongly associated with the asthmatic state. There is now evidence from a number of studies that it is maternal smoking that is important in predicting the risk or severity of asthma or wheezing (4-7, 9, 14-16). In our study we were unable to distinguish among current or past smoking by maternal caregiver or smoking in pregnancy by the biologic mother, as these measures were closely intercorrelated and all significantly associated with the child's asthmatic status. However, we confirmed that this is a direct effect of maternal smoking rather than a reflection of the number of smokers in the household.

We were unable to show an effect of passive smoke exposure on the precipitation of acute asthmatic attacks. For this purpose, we distinguished children visiting the ER with an acute attack at the time of recruitment from children with presumed similar asthmatic conditions who were not acute. We found no difference between the acute and nonacute groups when the CCR was used as a categorical measure (OR = 0.9), and self-reported smoking by the caregiver was actually more common among the nonacute group (OR = 0.6). Using CCR as a continuous variable, an elevation in the acute group was non-significant (46.2 versus 38.5 ng/mg).

The power of this second part of the study to show a twofold excess of exposure among acute asthmatic subjects

TABLE 6
SUBJECTS WITH COTININE/CREATININE RATIO $>$ 100 NG/MG

CDR	Age (yr)	Maternal Caregiver Smokes	Other Smokers at Home
Asthma			
745	3	No	Yes
335	5	Yes	Yes
270	4	No	No
238	3	No	No
186	5	Yes	No
140	3	Yes	Yes
118	9	Yes	Yes
Control			
468	3	Yes	No
232	5	No	No
136	7	Yes	No
130	5	Yes	Yes
128	8	No	Yes
112	12	No	No
102	9	Yes	Yes

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was less than 50%. However, conjecture that a larger sample might have shown such a significant positive association must be balanced against what was observed: no difference at all between the two groups with regard to cotinine measured categorically, and a negative association between maternal smoking status and acute asthma.

There were also some differences between the two asthmatic groups, which may have made it more difficult to show a positive association. Among the acute cases, only 65% had at some time previously attended the asthma clinic. Further, only 34% were on daily asthma medication at the time of recruitment compared to 80% of the asthma clinic cases. It is therefore possible that children attending the asthma clinic have more severe asthma. If greater severity of asthma is itself associated with passive smoking (14-16), the asthma clinic group may have had more passive smoke exposure to begin with. This would make it more difficult to show an elevated CCR in the acute asthma group even if they were subject to recent increases in exposure. It is possible that a real effect was thereby obscured. An alternative possibility is that treatment suppresses the effect of passive smoking. In such a case, the triggering effect of such exposure may be evident only in comparing acute cases with nonacute cases among children not on regular medication. Our numbers were too small to explore this further.

Use of cotinine as a biomarker of exposure enabled us to validate the reported smoking status of the maternal caregiver and to demonstrate nicotine absorption by the child. In addition, it provided an exposure measure free of interviewer bias.

The use of cotinine raised methodologic questions that need to be resolved. Other studies have shown that cotinine is measurable, sometimes at high levels, in children with no reported exposure at home (19). We found this also. We made use of the findings of Henderson and colleagues (21), who found that a cutoff level of 30 ng/mg optimally distinguished children exposed to tobacco smoke at home measured by air nicotine concentration and cigarette butts saved) from those unexposed.

We used cotinine to measure degree of recent exposure among acute and non-acute asthma. This presupposes that cotinine levels reflect the intensity of passive smoking. Because of interindividual differences in metabolism, however, the

variation in cotinine among children for a given exposure may be considerable. It also remains to be confirmed whether urinary cotinine levels in an individual child are stable over time so that a single measure reflects "average" exposure, or whether they are sufficiently sensitive to changes over and above this background exposure level to detect short-term ("peak") increases. Henderson's group, doing repeated measures, found stable urinary CCR levels over a period of 4 wk (21). The correlation coefficient found between average log CCR and average home nicotine concentration was 0.68. In contrast, Coulter and coworkers reported a wide variation in urinary CCR over a period of about 11 wk; their correlation coefficient between CCR and ambient nicotine was 0.15 (24). In view of the difficulties posed by these conflicting data, the hypothesis concerning acute exacerbation of asthma by environmental tobacco smoke needs a prospective study of asthmatic children, linking acute exacerbations of asthma to variations in exposure based both on repeated measures of cotinine and on some measure of environmental exposure.

We conclude that passive smoking by the mother or other maternal caregiver is associated with the asthmatic state among children. Given our observed odds ratio around 2.0, the high prevalence of both parental smoking and asthma makes this association a public health problem of considerable impact in this population.

We could not show that recent elevations in exposure to tobacco smoke triggered attacks of asthma requiring visits to the emergency room. Lack of statistical power, differences between acute and nonacute cases in medication use, and limitations in using a single cotinine measure may explain this finding rather than a true lack of effect. If our finding is valid, however, it may be because the mechanism of effect of maternal smoking on asthma is through increasing bronchial responsiveness in the child rather than by triggering bronchospasm. A number of studies have shown that bronchial responsiveness among asthmatic children is greater if the mother smokes (14-16, 25, 26). Such a mechanism is also compatible with the finding of Evans and colleagues (17) that the number of ER visits for acute asthma is increased if there is a smoker in the household. In contrast to these findings, those of general population studies have yet to clearly demonstrate an association between bronchial

responsiveness in children and parental smoking (25, 26).

The clinical implications of this study are clear. Maternal smoking in the households of asthmatic children in this population is all too common. Reduction of this potentially important risk factor should be the target of clinicians and health educators working with the families of these asthmatic children.

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